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Paraneoplastic ganglioradiculoneuritis in a cat with a plasma cell tumour

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Abstract

Case summary An 8-year-old neutered female domestic longhair cat was presented for investigation of a 48 h history of lethargy and pelvic limb ataxia. MRI of the spinal cord and vertebral column (C1 to sacrum) and brain was unremarkable. Lumbar cerebrospinal fluid analysis revealed pleocytosis and increased protein concentration. Thoracic radiographs and abdominal ultrasound were unremarkable. Anti-inflammatory doses of prednisolone were administered. Clinical deterioration occurred over the following 2 days, with the development of lower motor neuron deficits in both thoracic limbs. On repetition of the MRI, bilateral enlargement, T2-weighted hyperintensity, and marked contrast enhancement of the C7, C8 and T1 nerve roots, spinal nerves and brachial plexuses were observed. Infectious disease testing was negative. An immune-mediated inflammatory process was suspected and immunosuppressive doses of prednisolone were commenced. The clinical signs improved transiently, but marked deterioration occurred after 2 weeks. The patient was euthanased and a post-mortem examination was performed. A lymphocytic inflammatory infiltrate was detected in the C7, C8 and T1 nerve roots and dorsal root ganglia, and neoplastic plasma cells were identified in multiple organs. A diagnosis of non-cutaneous extramedullary plasmacytoma with multiorgan involvement and paraneoplastic ganglioradiculoneuritis was reached.

Relevance and novel information Paraneoplastic ganglioradiculoneuritis in association with a plasma cell neoplasia has not been previously reported in the cat and should be considered as a differential diagnosis for cats with clinical or imaging evidence of an inflammatory process affecting the nerve roots, spinal nerves or brachial plexuses.

Keywords: Neuritis; radiculoneuritis; paraneoplastic; plasma cell tumour; plasmacytoma

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Introduction

Paraneoplastic neurological syndromes (PNNSs) occur when antibodies are generated targeting antigens common to both a tumour and components of the nervous system.¹ PNNSs are well documented in humans and can cause a variety of severe neurological deficits.² These may become apparent long before the development of clinical signs directly attributable to the tumour.^{2–4} PNNSs have been sporadically reported in dogs with various tumours,^{5–8} and in a cat with lymphoma.⁹ To our knowledge, this is the first report of a PNNS in association with plasma cell neoplasia in the cat.

Case description

An 8-year-old neutered female domestic longhair cat was presented for investigation of a 48 h history

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of progressive lethargy and pelvic limb general proprioceptive ataxia. The general physical examination revealed tachypnoea (56 breaths/min) and no other abnormalities. The cat's body weight was 5.8 kg. Neurological examination revealed ambulatory paraparesis, general proprioceptive ataxia in both pelvic limbs, mildly delayed postural reactions in the left pelvic limb and suspected discomfort on handling, although no clear focus of pain could be identified. The remainder of the neurological examination, comprising assessment of mentation, behaviour, posture, segmental spinal reflexes and cranial nerves, was unremarkable. The neuroanatomical localisation was to the T3–L3 spinal cord segments.

Haematology and comprehensive biochemistry profiles were performed, and no significant abnormalities were detected apart from elevated creatine kinase (1668 IU/l; reference interval [RI] 70–190). Owing to tachypnoea noted on initial presentation, as well as the discomfort that could not be localised, radiographs of the thorax, abdomen, vertebral column, hips and pelvis were obtained, which were all unremarkable.

MRI was performed using a 1.5 Tesla scanner (Signa EchoSpeed; GE Healthcare), initially of the thoracolumbar spinal cord and vertebral column. No lesions were seen, and therefore the MRI was extended to include the rest of the vertebral column and the brain. No abnormalities were identified, apart from a mildly enlarged presternal lymph node. Immediately following MRI, cerebrospinal fluid (CSF) samples were obtained from both the cerebellomedullary cistern and lumbar subarachnoid space. The

cerebellomedullary sample was cytologically and biochemically within normal limits, whereas analysis of the lumbar sample showed elevations in both nucleated cell count (11/ μ l; RI <8) and protein concentration (1.77 g/l; RI 0.00–0.45) with a normal erythrocyte count (41/ μ l; RI <250). Nucleated cells comprised 70% lymphocytes, most of which were small with occasional reactive forms, 20% large mononuclear cells and 10% non-degenerate neutrophils. CSF was also submitted for PCR testing for coronavirus, herpesvirus and *Toxoplasma gondii*. A patient-side ELISA (SNAP Combo FIV/FelV Combo; IDEXX) was negative for feline leukaemia virus antigen and feline immunodeficiency virus (FIV) antibodies. A blood sample for serology for *T gondii* antibodies was submitted. Abdominal ultrasound and urinalysis performed on a sample obtained by cystocentesis were unremarkable.

Considering the rapidity of the onset of the clinical signs, their progressive nature, the absence of visible lesions on MRI and the abnormalities identified on CSF analysis, an inflammatory process was considered most likely. Prednisolone was commenced at anti-inflammatory doses (0.4 mg/kg q12h), pending results of infectious disease testing. The patient's neurological status markedly deteriorated over the following 48 h. The cat became non-ambulatory tetraparetic, with reduced withdrawal reflexes in both thoracic limbs, leading to a neurolocalisation to the C6–T2 spinal cord segments.

MRI of the spinal cord and vertebral column from the cervicothoracic junction to the T7 vertebrae was repeated (Figures 1 and 2). Images were obtained in

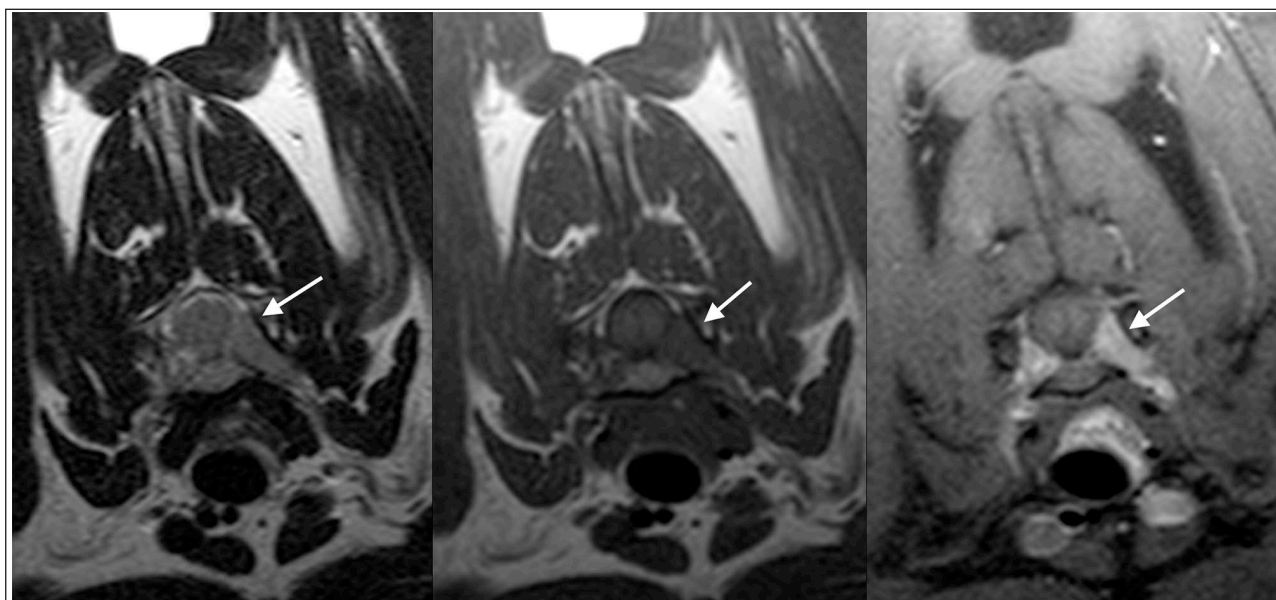


Figure 1 Transverse T2-weighted (T2W; left), T1-weighted (T1W; middle) and T1W post-gadolinium with fat suppression (right) magnetic resonance images at the level of the C7–T1 intervertebral foramen. The C8 nerve roots and spinal nerves are enlarged and hyperintense in T2W, hypointense in T1W and markedly contrast enhancing in T1W post-gadolinium sequences, particularly on the left side, indicated by the arrows. Note that the patient's left side is on the right side

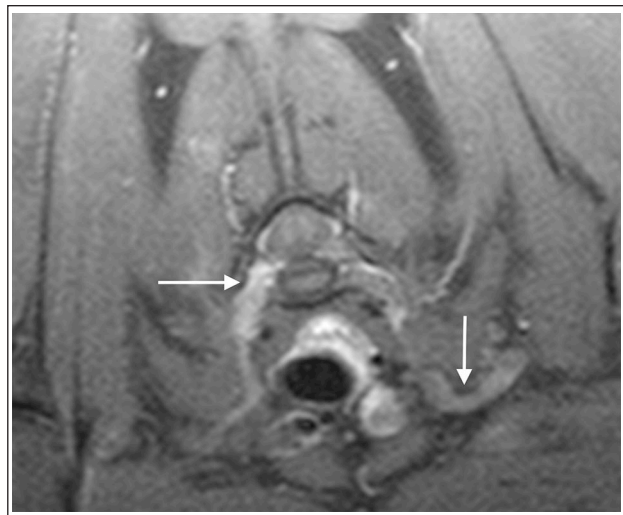


Figure 2 Transverse T1W post-gadolinium image with fat suppression at the level of the brachial plexuses. The horizontal arrow indicates the enlarged and markedly contrast-enhancing right C8 spinal nerve. The vertical arrow indicates the enlarged and moderately contrast-enhancing left brachial plexus. Note that the patient's left side is on the right side

T2-weighted (T2W) sequences in dorsal, sagittal and transverse planes, in T1-weighted sequences in sagittal and transverse planes, in STIR (short tau inversion recovery) sequence in a dorsal plane and post-gadolinium (0.1 mmol/kg IV [Gadovist, Bayer]) in fat-saturated T1-weighted (T1W) sequences in transverse and sagittal planes. The transverse sequences showed bilateral, moderate, diffuse thickening, with T2W hyperintensity and T1W hypointensity of the C7, C8 and T1 spinal nerves, with the greatest enlargement at the C8 spinal nerve on the left side. The thickening extended from the dorsal and ventral nerve roots, with mild left-sided cord compression, through the intervertebral foramina and to the brachial plexuses, which were also mildly enlarged on both sides, more so on the left. On post-contrast T1W images, the thickened spinal nerves showed marked contrast enhancement, which was present to a milder degree in both brachial plexuses.

CSF was again obtained from the lumbar subarachnoid space. Analysis revealed albuminocytological dissociation. The nucleated cell count was $2/\mu\text{l}$ (RI 0–8) and total protein was 1.8g/l (RI 0.00–0.45). At this stage, important differential diagnoses included hypertrophic neuritis and neoplasia (eg, lymphoma). The previously submitted tests for infectious disease were all negative. The prednisolone dosage was increased to an immunosuppressive dosage (1.7 mg/kg PO q12h) to treat the possible hypertrophic neuritis. Clinical improvement occurred within 48h. The patient became ambulatory but remained tetraparetic, and was discharged into its owners' care.

Two weeks later, rapid and marked deterioration occurred over 48h. The cat became anorexic and lethargic. On reassessment, dyspnoea, nasal discharge, tachycardia and a paradoxical breathing pattern were present. The neurological examination revealed obtundation, generalised weakness and non-ambulatory tetraparesis. The owners requested euthanasia without further diagnostic investigations and consented to a post-mortem examination.

Macroscopic post-mortem findings included mild ascites, mild hydrothorax, mild multifocal ulcerative gastritis and the presence of multifocal, round, approximately 3 mm diameter white/yellow lesions in the lungs, liver, kidney, perirenal adipose tissue and urinary bladder. Examination of the nerve roots at the level of the cervical intumescence of the spinal cord revealed diffuse, mild-to-moderate thickening with white/yellow discolouration.

Histopathology revealed a malignant round-cell neoplastic proliferation in the liver, kidney, urinary bladder, peritoneal cavity and stomach, characterised by multifocal accumulations of round cells, arranged in sheets, supported by a scant amount of fibrovascular stroma. The neoplastic cells had distinct borders, a moderate amount of eosinophilic cytoplasm and contained one round-to-oval nucleus with prominent nucleoli. Anisokaryosis and anisocytosis were moderate to severe, and several multinucleated cells were identified. On average, there were three mitoses per high-power field with atypical mitotic figures. Atypical round cells were also identified in the lumen of several vessels in the fat adjacent to the lumbosacral spinal cord.

In the cervical intumescence of the spinal cord within the white matter, some axons were mildly swollen and others were replaced by activated macrophages. In the dorsal root ganglia at the level of the cervical intumescence, neuronal degeneration was present with central chromatolysis and accumulation of lipofuscin with concomitant multifocal increase in the number of glial cells and infiltration of small lymphocytes. The lymphocytic infiltration was extending into the nerve roots and spinal nerves, without evidence of the previously described atypical round-cell population. This was therefore considered to be part of a reactive, potentially paraneoplastic, inflammatory process.

On immunohistochemical analysis, the neoplastic cells stained positive for MUM1 (a plasma cell marker). No MUM1-positive cells were detected in the spinal nerve roots or spinal nerves. The final diagnosis was non-cutaneous extramedullary plasmacytoma with multiorgan involvement¹⁰ and paraneoplastic ganglioradiculoneuritis.

Discussion

Possible aetiologies of peripheral neuropathies in cats include hereditary disorders, and infectious, endocrine, nutritional, toxic and idiopathic diseases.^{11,12} In addition,

neoplasia can affect the peripheral nervous system either by direct infiltration; for example, in cases of nerve sheath tumour, meningioma (affecting nerve roots) or lymphoma, or by paraneoplastic effect. A paraneoplastic peripheral neuropathy, characterised by demyelination, axonal degeneration and muscle denervation has been reported in a cat with renal lymphoma.⁹ Paraneoplastic peripheral neuropathies have also been sporadically described in dogs, in association with insulinoma,^{5,6} lymphoma,^{6,7} multiple myeloma,⁸ bronchogenic carcinoma, melanoma, osteosarcoma, thyroid carcinoma, mammary carcinoma, squamous cell carcinoma, myxosarcoma, nasal adenocarcinoma and mast cell tumours.⁶ The most common finding on biopsy of affected nerves is demyelination/remyelination, although axonal degeneration has also been reported.⁵⁻⁷ Paraneoplastic neuropathies have been reported in the human literature in association with numerous neoplastic processes, including various types of lung cancer, neuroblastoma, prostatic carcinoma, ovarian cancer, thymoma, lymphoma, breast cancer¹ and plasma cell tumours.¹³ Polyradiculoneuropathy is an important component of the human paraneoplastic syndrome that occurs due to an underlying plasma cell disorder;¹³ demyelination is a prominent feature.¹

PNNs in humans can affect any part of the central or peripheral nervous systems, including components as diverse as the optic nerves, vestibular apparatus¹⁴ and enteric nervous system.¹⁵ They can become apparent months, or even years, before any clinical signs directly attributable to the tumour itself are observed²⁻⁴ and frequently cause dramatic and rapidly progressive neurological dysfunction.^{1,2} PNNs are immune-mediated erroneous attacks on components of the central or peripheral nervous systems, originally intended to target the tumour itself.¹ The immune-mediated pathogenic effect in PNNs is driven by antibodies that target antigens expressed concurrently by the tumour and the nervous system.² Such antigens are particularly prevalent in tumours of neuroectodermal lineage, such as small cell lung cancer in people.¹ Some antibodies may target neuronal cell-surface antigens; for example, the *N*-methyl-D-aspartate receptor, whereas others, known as onconeural antibodies, target intracellular antigens.^{2,3} Systematic screening for the presence of onconeural antibodies in the serum and/or CSF is possible in human medicine. Pathogenic effects in PNNs include cytotoxic T-cell-mediated neuronal cell death and cross-linking, and internalisation of surface antigens, leading to cell dysfunction or inactivation without cell death.¹ In PNNs affecting the central nervous system in people, nerve roots or spinal sensory ganglia, inflammatory changes in CSF are found in around 90% of cases,¹ as were found in this cat.

Paraneoplastic signs can resolve following definitive treatment of the tumour; adjunctive immunosuppressive treatment may also be utilised.¹ In our case,

immunosuppressive treatment resulted in a transient clinical improvement, although the clinical signs quickly relapsed. The response of PNNs to treatment of the underlying neoplastic process is not well documented in veterinary medicine, although resolution of PNNs have been reported in a Brittany Spaniel with a bronchogenic adenoma and mammary mass following surgical resection¹⁶ and in a German Shepherd dog with multiple myeloma following chemotherapy.⁸ Owing to the lack of a definitive ante-mortem diagnosis in our case, no attempt to treat the neoplasia could be made. It remains unknown, therefore, whether this PNN would have resolved had the underlying neoplasia been treated.

Following the MRI finding of bilateral nerve root and spinal nerve enlargement, important differential diagnoses included hypertrophic neuritis and neoplasia. Hypertrophic neuritis has been reported in two cats.^{17,18} In both cases the nerve roots of the cervical intumescence and brachial plexuses were involved, as was the case in our cat. In one case,¹⁸ PCR performed on peripheral nervous tissue was positive for FIV; a causative link between FIV and the neuritis was considered possible. Neoplasias that may give a similar MRI appearance include nerve sheath tumour (NST)¹⁹ and lymphoma.²⁰ Owing to the bilateral, although slightly asymmetrical, imaging abnormalities, NST was considered less likely than lymphoma, which can show great diversity in its clinical and imaging characteristics.²¹ MRI characteristics of brachial plexus lymphoma in a cat have been described as a T1 and T2 hyperintense mass associated with the C6, C7, C8 and T1 spinal nerves;²⁰ these findings bear comparison with the MRI features of our case, although the lesions in our patient were spread more diffusely throughout the nerves without the dramatic, focal enlargement present in the lymphoma case. This case report demonstrates that inflammatory lesions of paraneoplastic origin should also be considered as a differential diagnosis in the face of such MRI findings.

The difficulty in proving cause and effect in PNNs has been discussed.³ In humans, such a diagnosis depends on both common association between a given cancer type and PNNs, and detection of antibodies in serum and/or CSF that bind neoplastic and nervous tissue.³ In veterinary medicine, the diagnosis is presumptive and relies on demonstrating the concurrent presence of a neoplastic process and neurological deficits without any other demonstrable cause, as was achieved in this cat.

Electrodiagnostic investigations were not performed in this case. These may have yielded interesting information regarding functional compromise of the affected nerves, in addition to the structural changes identified on MRI, or revealed subclinical involvement of other nerves, and should ideally be performed in similar cases.

Conclusions

Ganglioradiculoneuritis of presumed paraneoplastic origin was diagnosed in a cat with a non-cutaneous extramedullary plasmacytoma with multiorgan involvement. This led to marked and progressive neurological deficits, which occurred without overt ante-mortem evidence of a neoplastic process. A PNNS should be considered in cats with imaging or histological evidence of inflammation within the nerve roots or nerves. Specifically, plasma cell neoplasia should be recognised as a possible trigger for the inflammatory process. Thorough investigation for underlying neoplastic pathology is recommended in such cases.

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Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

Informed consent Informed consent (either written or verbal) was obtained from the owner or legal custodian of all animal(s) described in this work for the procedure(s) undertaken (either prospective or retrospective studies). No animal or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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